

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D U 8 JUL 2005

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Applicant's or agent's file reference CHL-479-03		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/B2004/000981		International filing date (day/month/year) 01.04.2004	Priority date (day/month/year) 13.05.2003	
International Patent Classification (IPC) or national classification and IPC C07D215/56				
Applicant CADILA HEALTHCARE LIMITED				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in Item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 03.01.2005		Date of completion of this report 07.07.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Weisbrod, T Telephone No. +49 89 2399-		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2004/000981

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-10 as originally filed

Claims, Numbers

1-20 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-20
	No: Claims	
Inventive step (IS)	Yes: Claims	1-20
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-20
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

The application is directed to a process for the preparation of the omega form of anhydrous gatifloxacin (independent claims 1 and 2, and dependent claims 3-20).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: US-B-6 413 9691, 2 July 2002; cited in the application.

D2: WO 03/086402 A, 23 October 2003; cited in the application.

D3: US-A-5 043 450, 27 August 1991; cited in the application.

D2 was published after the priority date. Under the presumption that the priority is valid for the claimed matter the said document is not considered as prior art under Rule 64.1 PCT.

2 Novelty.

2.1 D1 relates to 12 different polymorphs respectively pseudopolymorphs of gatifloxacin and is, particularly, directed to the pentahydrate. In this context, the documents discloses also omega gatifloxacin as a high-temperature form accessible from two other forms at 170 °C. A solvent-mediated or crystallisation process for the preparation of omega gatifloxacin is not disclosed in D1. The present claimed processes are thus novel vis-à-vis D1.

D3 describes the preparation of gatifloxacin by reacting the respective starting materials in DMSO according to process step (a) of present claim 2, removing the solvent in vacuo, purifying the residue by chromatography, followed by recrystallisation from methanol to afford the title compound with a melting point of 162 °C. In view of the phase transformation temperature of 170 °C for the preparation of omega gatifloxacin according to D1, and its melting point disclosed in D2 (188.35 °C, figure 3, anhydrous form I), the gatifloxacin prepared in D3 is different from omega gatifloxacin. D3 is thus not relevant to the question of novelty of the

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present application.

2.2 **D2** relates to two anhydrous polymorphs of gatifloxacin, of which the anhydrous form I corresponds with the omega form, according to the present application (cf. page 9, last paragraph, and page 10). According to **D2** omega respectively form I of gatifloxacin is prepared from gatifloxacin hydrate by (i) azeotropic removal of water from gatifloxacin in refluxing toluene, (ii) cooling for crystallisation, (iii) isolation of the precipitate, washing and drying, (iv) dissolving the dried product in refluxing acetone, (v) stripping off a certain amount of solvent, followed by cooling, (vi) and isolating, washing and drying to afford omega gatifloxacin. The present claimed processes are at least novel over the process of **D2** through the process steps (a) to (d) of claim 1 and the corresponding steps of claim 2.

3 Inventive Step

3.1 The application describes the preparation of omega gatifloxacin by crystallisation involving the steps of (a) dissolving raw gatifloxacin in a methanolic solution of potassium hydroxide, (b) filtering the solution, (c) neutralising the filtrate with acetic acid to cause crystallisation of precipitation, (d) refluxing the suspension followed by cooling and (e) isolation (examples 1 and 2). In addition, the application shows the crystallisation of omega gatifloxacin from cyclohexane (example 6), methanol (examples 3 and 5), and aqueous methanol (example 4).

3.2 In view of **D1**, at present considered as most relevant state of the art, the problem underlying the application is seen in the provision of alternative processes for the preparation of omega gatifloxacin. Since the document **D1** discloses omega gatifloxacin merely as a high temperature form of gatifloxacin that had been obtained by a phase transformation at 170 °C, the present claimed processes do not appear obvious in view of **D1** and **D2**, such that the present claims 1-20 seem to involve an inventive step.

Re Item VI

Certain documents cited

Certain published documents

Application No
Patent No

Publication date
(day/month/year)

Filing date
(day/month/year)

Priority date (valid claim)
(day/month/year)

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WO 03/086402 A1

23.10.2003

07.04.2003

08.04.2002

Re Item VII

Certain defects in the international application

The application does not comply with the requirements of Article 6 PCT for the following reasons.

- 1 According to example 1 raw gatifloxacin is prepared by reacting the starting materials in DMSO, diluting the mixture after completed reaction with i-PrOH, cooling, and isolating the product by filtration. Accordingly, gatifloxacin is crystallised or precipitated from a DMSO/i-PrOH mixture. This crystallisation or precipitation operation is, however, not properly reflected by the formulation of step (b) in claim 2, because the vague phrase "adding a suitable solvent to the above reaction mass" neither indicates any function of this process step nor any purpose for which the solvent should be suitable. Consequently, the claim is not clearly defined.
- 2 The dependency of the claims 3 to 7 seems to be erroneous in view of the process steps to which these claims refer. The same applies for claim 20 which refers to itself.

Re Item VIII

Certain observations on the international application

The reference to form II of **D2** on page 9, last paragraph, of the application appears to be erroneous and it appears that form I has been intended.